REMARKS

This responds to the Office Action mailed May 4, 2005, and the references cited therewith. Claims 1, 11 and 26 are amended to clarify the subject matter that applicants regard as their invention and to correct a typographical error in the structure of Formula I in Claim 1. The error was unintentional and the appropriate correction is respectfully requested. As a result, claims 1, 3-4, 11, 13-14, 26-29, 34 and 35 are now pending in this application. No new subject matter is added.

§103 Rejection of the Claims

Claims 1, 3, 4, 13 and 34 were rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Rephaeli (U.S. Patent No. 5,939,455 "the '455 patent"). The Examiner asserts that it would have been obvious to have chosen etodolac from one list in the '455 patent and multiple myeloma from another list, given the unambiguous, specific, and discrete disclosure of each. To the extent that this rejection may be maintained with respect to the pending claims, it is respectfully traversed.

The Examiner has the burden under 35 U.S.C. § 103 to establish a *prima facie* case of obviousness. *In re Fine*, 837 F.2d 1071, 1074, 5 U.S.P.Q.2d (BNA) 1596, 1598 (Fed. Cir. 1988). In combining prior art references to construct a *prima facie* case, the Examiner must show some objective teaching in the prior art or some knowledge generally available to one of ordinary skill in the art that would lead an individual to combine the relevant teaching of the references. *Id.* The M.P.E.P. contains explicit direction to the Examiner that agrees with the *In re Fine* court:

> To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. *M.P.E.P.* § 2142 (citing *In re Vaeck*, 947 F.2d 488, 20 U.S.P.Q.2d (BNA) 1438 (Fed. Cir. 1991)). See also *In re Rouffet*, 47 USPQ2d 1453. The court in *Rouffet* stated that "even when the level of skill in the art is high, the Board must identify specifically the principle, known to one of ordinary skill that suggests the claimed combination." *Rouffet* at 1459. Further, even if the

> allegation of obviousness is based on a single prior art reference, there must be a showing of a suggestion or motivation to modify the teachings of the single reference. *B.F. Goodrich Co. v. Aircraft Breaking Sys. Corp.*, 37 USPQ2d 1314, 1318 (Fed. Cir. 1996).

The Rephaeli '455 patent in column 5, lines 34 and 35, discloses use of butyric acid based chemotherapeutic drugs in treating cancers, including myeloma. The '455 patent discloses and claims a method to augment the therapeutic activity of a large genus including an "an oxyalkylene containing compound, butyric acid, a butyric acid salt or butyric acid derivatives." Col. 1, lines 61-63; Col. 4, lines 54-60. The '455 patent discloses that the β-oxidation of these active agents can be inhibited with NSAIDs, including etodolac. Col. 4, lines 23-27. The Examiner is urged to consider that the patent does not ascribe any therapeutic effect against the cancer cells to the NSAIDs – these are used to protect the active ingredient from degradation.

The Examiner is requested to consider that all of the claims recite that the compound of formula I, *e.g.*, the etodolac or analog, or 1-R(-)-etodolac is itself administered in an amount that is per se effective to kill cancer cells. This is not disclosed or suggested in the '455 patent.

Furthermore, the '455 patent concerns methods of augmenting the activity of butyric acid derivatives by administering such derivatives with inhibitors of β-oxidation. The inventor of the '455 patent discloses that by administering butyric acid with a β-oxidation inhibitor the half-lives of a butyric acid compound may be augmented because they would not be oxidized as quickly in the presence of a β-oxidation inhibitor. Normally butyric acid is metabolized very quickly by β-oxidation in the mitochondria.

Thus, in order for one of ordinary skill in the art to find the presently-claimed invention obvious in view of the full disclosure of the '455 patent, the art worker would be required to ignore the explicit teachings that the β-oxidation inhibitor, such as etodolac, including R(-) etodolac, functions to protect the active agent from degradation and use it as the active agent to inhibit multiple myeloma cells. It is respectfully submitted that there is no teaching in the '455 patent that would reasonably teach the art worker to believe that this should even be attempted, much less that it would be accomplished. Furthermore, there is even less in the cited document that would lead the art worker to believe that the β-oxidation inhibitor, such as etodolac, would

itself maintain the viability of normal cells while killing the cancer cells, as recited in the instant claims.

Accordingly, it is respectfully submitted that the present claims are not obvious in view of the '455 patent, and withdrawal of this rejection is respectfully requested.

Claims 11, 14, 26-29 and 35 are rejected under 35 USC § 103(a) as being unpatentable over Rephaeli (U. S. Patent No. 5,939,455 "the '455 patent") in view of Wechter *et al.* (WO 98/09603 "the '603 application"). The Examiner asserts that the '455 patent would have been obvious to use the R-enantiomer of etodolac" with butyric acid based chemotherapeutic drugs for the treatment of cancer." To the extent the rejection applies to the amended claims, Applicants respectfully traverse.

The requirements for establishing a proper obviousness rejection are stated above.

The Examiner further asserts that the '603 application discloses the use of the R-enantiomers, which have lower side effects. However, as the Examiner admits this disclosure fails to remedy the deficiencies of the '455 patent, because the '603 application fails to disclose the treatment of multiple myeloma. In addition, the combination fails because the '455 patent states that the NSAIDS will function as an inhibitor of β-oxidation and not that a NSAID will be suitable to kill cancer cells. There is no teaching or suggestion to combine the disclosure of the '455 patent with the disclosure of the '603 application. Accordingly, a person skilled in the art would not have been lead to Applicants' invention from these documents either alone or in combination.

In addition, the '455 patent and the '603 application fail to teach or suggest the ability of etodolac to selectively kill cancerous cells. There is no guidance in either the '455 patent or the '603 application regarding the appropriate concentrations of R-NSAIDS needed to kill cancer cells. In fact the '603 application is silent on this point. Applicants were the first to disclose the concentrations of etodolac needed to kill cancer cells (see, for example Fig. 5 of the present application). These concentrations are not found or disclosed in the '603 patent application.

The '603 application discloses that any R-NSAID can be used to treat neoplastic disease. Further, the '603 application discloses that for the treatment of neoplastic disease the preferred daily dose should be about 1.0 mg to about 2000 mg in single or divided doses (see last line of

page 11 bridging to page 12 of the '603 specification). In Example of 1 of the '603 application, Wechter et al. used 6.3 mg/Kg/day of R-flurbiprofen to obtain a reduction in the labeling index of crypt cells from rats. The '603 application provides no information regarding the dosing needed for other NSAIDS to obtain an anti-proliferative effect yet alone a killing effect. Because the '603 application claims any R-NSAID, one of ordinary skill in the art is left with potentially an unlimited number of dosing ranges to test to determine the anti-proliferative concentrations of a particular R-NSAID.

In summary, the cited documents fail to disclose all of the elements of the claimed invention (killing of cancer cells) in addition it fails to provide any suggestion, teaching, or motivation to modify its teachings to arrive at the present invention.

Thus, it is respectfully requested that this rejection be withdrawn.

Obviousness-Type Double Patenting Rejection

Claims 1, 3, 4, 11, 13, 14, 26-29, 34 and 35 were provisionally rejected under the judicially created doctrine of obviousness-type double patenting rejection as being unpatentable over claims 10, 13 and 15 of co-pending U.S. Application No. 09/634,207 or unpatentable over claims 16-20 of co-pending U.S. Application No. 09/634,207 in view of Spiegelman et al. (U.S. Patent No. 6,552,055.). Applicants respectfully traverse the rejection.

Applicant respectfully submits that the co-pending U.S. Application is not yet allowed, hence the provisional rejection is premature. In addition, applicants disagree with the Examiner. However, in order to expedite the allowance of the instant claims, while not conceding the obviousness of any number of the pending claims over the claims of the '207 application claims, should the instant application be allowed after the allowance of the aforementioned co-pending application (Serial No. 09/634,207), an appropriate terminal disclaimer will be filed in the instant application.

Claims 1, 3, 4, 11, 13, 14, 26-29, 34 and 35 were provisionally rejected under the judicially created doctrine of obviousness-type double patenting rejection as allegedly being unpatentable over claims 1-9 and 12-23 of co-pending U.S. Application Serial No.

10/682,790 in view of Spiegelman et al. (U.S. Patent No. 6,552,055.). Applicants respectfully traverse the rejection.

Applicant respectfully submits that co-pending U.S. Application Serial No. 10/682,790 is not yet allowed, hence the rejection is premature. In addition, the obviousness type double patenting rejection in view of the '055 Spiegelman patent is improper as argued in the previous section for rejections under 35 USC § 103(a). Applicants submit that there is no motivation to combine the claims of U.S. Application Serial No. 10/682,790 with the Spiegelman patent. Accordingly, reconsideration and removal of the instant rejection is respectfully requested.

CONCLUSION

Applicants respectfully submit that the claims are in condition for allowance, and notification to that effect is earnestly requested. The Examiner is invited to telephone Applicants' attorney at (612) 373-6968 to facilitate prosecution of this application.

If necessary, please charge any additional fees or credit overpayment to Deposit Account No. 19-0743.

Respectfully submitted,

DENNIS A. CARSON ET AL.

By their Representatives,

SCHWEGMAN, LUNDBERG, WOESSNER & KLUTH, P.A.
P.O. Box 2938
Minneapolis, MN 55402
(612) 373-6900

Date 6 September 2005

By _____
Katharine A. Jackson Huebsch
Reg. No. 47,670

CERTIFICATE UNDER 37 CFR 1.8: The undersigned hereby certifies that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail, in an envelope addressed to: Mail Stop Amendment, Commissioner of Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on this 6 day of September, 2005.

LISA POSORSKE
Name

Lisa Posorske
Signature